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Remarks

Claims 13-33 are pending in the subject application. By this Amendment, Applicants have canceled claims 13-33 and added new claim 34. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claim 34 is currently before the Examiner. Favorable consideration of the pending claim is respectfully requested.

As an initial matter, Applicants gratefully acknowledge the Examiner's withdrawal of all the objections and rejections in the previous Action.

Claims 13-33 are rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification and as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action indicates that while the subject specification is enabled for a method of orally administering a RANTES polypeptide of SEQ ID NO: 1 or SEQ ID NO: 5 for the treatment of multiple sclerosis, it does not reasonably provide enablement for oral administration of any other RANTES polypeptide. The Office Action argues that the as-filed specification fails to provide adequate written description of the genus of polypeptides embraced by the claims with respect to RANTES polypeptides having at least 90% homology to the wild-type RANTES polypeptides. Applicants respectfully assert that the claims are enabled by the subject specification and that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that they had possession of the claimed invention. However, in order to expedite prosecution of the subject application to completion, the claim has been amended to recite a method of orally administering a RANTES polypeptide of SEQ ID NO: 1 for treating multiple sclerosis and it is believed that the issues directed to the previously pending claims are now moot. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 13-16 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully assert that the claims as filed are definite. However, as these claims have been canceled, it is believed that this rejection is moot and reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 13-33 are rejected under 35 U.S.C. § 103(a) as obvious over Proudfoot *et al.* (2001) and Lusso and Polo (WO 99/33989) in view of Czaplewski *et al.* (U.S. Patent No. 5,965,697). The Office Action indicates that Proudfoot *et al.* teach a RANTES polypeptide produced by a mutation of amino acids 44, 45 and 47 and specifically teach a RANTES polypeptide which is "equivalent to the polypeptide of SEQ ID NO: 1". Lusso and Polo were cited, according to the Office Action, for their teaching of a RANTES polypeptide that has at least 90% identity to the wild-type RANTES polypeptide. The Office Action admits that both the Proudfoot *et al.* and the Lusso and Polo publications are silent with respect to the oral administration of RANTES polypeptides to an individual. The Office Action cites to Czaplewski *et al.* for a teaching that RANTES polypeptides can be orally administered for the treatment of viral diseases, such as HIV. The Office Action also argues that Czaplewski *et al.* teach the treatment of multiple sclerosis comprising the administration of RANTES (citing to column 2, lines 10-19). Applicants respectfully traverse this rejection.

As the Patent Office is aware, a patent claim is obvious when the differences between the claimed invention and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103; *see also Graham v. John Deere Co.*, 383 U.S. 1, 14 (1966); *In re Dembiczak*, 175 F.3d 994, 998 (Fed. Cir. 1999). While obviousness is ultimately a legal determination, it is based on several underlying issues of fact, namely: (1) the scope and content of the prior art; (2) the level of skill of a person of ordinary skill in the art; (3) the differences between the claimed invention and the teachings of the prior art; and (4) the extent of any objective indicia of non-obviousness. *See Graham*, 383 U.S. at 17-18. When obviousness is based on the teachings of multiple prior art references, it is incumbent upon the Patent Office to establish some "suggestion, teaching, or motivation" that would have led a person of ordinary skill in the art to combine the relevant prior art teachings in the manner claimed. *See In re Kahn*, 441 F.3d 977, 987 (Fed. Cir. 2006). The Patent Office's reviewing court has stated, "Our case law makes clear that the best defense against the subtle but powerful attraction of a **hindsight**-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *Dembiczak*, 175 F.3d at 999. This is because "[c]ombining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for

piecing together the prior art to defeat patentability-the essence of **hindsight**." *Dembiczak*, 175 F.3d at 999. Therefore, the Federal Circuit has consistently held that a person of ordinary skill in the art must not only have had some motivation to combine the prior art teachings, but some motivation to combine the prior art teachings in the particular manner claimed. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000) ("Particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination *in the manner claimed*." (emphasis added)); *In re Rouffet*, 149 F.3d 1350, 1357 (Fed.Cir.1998) ("In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination *in the manner claimed*." (emphasis added)).

Applicants respectfully assert that the claimed invention is not obvious over the cited references, regardless of whether the references are taken alone or in combination. Applicants respectfully assert that the Czaplewski *et al.* reference relates to disaggregated RANTES mutants, which are useful in HIV treatment. In referring to the prior art, this reference mentions that RANTES may be involved in multiple sclerosis; however, it fails to give guidance on any mutants that may be useful for the treatment of this disease. Indeed, Czaplewski *et al.* fail to teach that the mutants disclosed within that patent can be used for the treatment of multiple sclerosis. Rather, the patent teaches that the disaggregated hRANTES polypeptides disclosed therein can be used to treat inflammatory diseases and conditions such as: transplant rejection, atherosclerosis, arthritis, atopic dermatitis, airway inflammatory disorders such as Rous Sarcoma Virus-induced bronchiolitis, delayed type hypersensitivity (DTH) reactions, glomerular nephritis, asthma, endometriosis and cancers (such as, T cell lymphomas, renal cell carcinoma and Wilms' tumors) (see, for example, column 11, line 14). Notably absent from the list of diseases taught in the patent is multiple sclerosis. Thus, it is respectfully submitted that Czaplewski *et al.* would not have taught, suggested, or motivated one skilled in the art to orally administer the claimed RANTES polypeptide to an individual having multiple sclerosis. Thus, as Czaplewski *et al.* fail to teach RANTES mutants according to the subject application or the oral administration of RANTES mutants for the treatment of multiple sclerosis (only discussing multiple sclerosis in the discussion of background art at

column 2), Applicants respectfully submit that a *prima facie* case of obviousness has not been established with respect to the claimed invention.

While Applicants respectfully submit that a *prima facie* case of obviousness has not been established by the Patent Office, Applicants further submit that oral administration of the claimed RANTES homolog (SEQ ID NO: 1) resulted in increased bioavailability and effectiveness as compared to wild-type RANTES polypeptides and/or the same RANTES homolog (SEQ ID NO: 1) provided to a test subject via a different route of administration. It is respectfully submitted that such increased bioavailability and effectiveness would not have been expected by one skilled in the art in view of the teachings of the cited references and that the examples and data provided in the as-filed specification provide evidence pertaining to the non-obviousness of the claimed invention.

The specification clearly indicates that the RANTES homolog of SEQ ID NO: 1, having reduced GAG-binding activity and non-conservative substitutions in the 40's dibasic site, exhibits increased bioavailability and better efficacy when administered orally (see, for example, Results, pages 23-24 of the as-filed specification). As indicated therein, the RANTES homolog of SEQ ID NO: 1 is able to exert an antagonistic activity for a longer period of time when administered orally. The Example also indicates that the RANTES homolog of SEQ ID NO: 1 was able to inhibit cell recruitment in the peritoneal cavity of animals when administered orally and intraperitoneally. However, a time course study indicated that the orally administered RANTES homolog (SEQ ID NO: 1) inhibited the recruitment of peritoneal cells by RANTES for up to 24 hours whereas the same intraperitoneally administered RANTES homolog was able to inhibit the recruitment of cells for a period of less than 8 hours. Thus, the oral administration of the RANTES homolog of SEQ ID NO: 1 has been demonstrated to have unexpectedly better bioavailability and/or ability to inhibit the recruitment of cells as compared to other routes of administration (*e.g.*, intraperitoneal administration) for the same RANTES homolog. Applicants respectfully submit that this is an unexpected benefit of the oral administration of the claimed RANTES homologs and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 13-33 are provisionally rejected under the judicially created doctrine of "obviousness-type" double patenting over claims 11, 12, 15, 16, and 19 of co-pending Application No. 10/540,234. While Applicants acknowledge that a Terminal Disclaimer can be filed to overcome this rejection, it

is submitted that a double patenting rejection of the obviousness-type is analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103, except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 U.S.P.Q. 29 (C.C.P.A. 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 U.S.P.Q.2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985). Accordingly, the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. 103(a) rejection and the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) are applied for establishing a background for determining obviousness under 35 U.S.C. 103, including the consideration of any indicia of non-obviousness, when making the obvious-type double patenting analysis (emphasis added).

In this instance, Applicants respectfully submit that the as-filed specification provides evidence pertaining to the non-obviousness of the claimed invention and that the application of an obviousness-type double patenting rejection in this matter is inappropriate. For example, the specification clearly indicates that the RANTES homolog of SEQ ID NO: 1 has increased bioavailability and better efficacy when administered orally (see, for example, Results, pages 23-24 of the as-filed specification). As indicated therein, these types of RANTES homologs were able to exert an antagonistic activity for a longer period of time when administered orally as compared to other routes of administration. The data and discussion contained at pages 23-24 also indicate, in a time course study, that orally administering the RANTES homolog as set forth in SEQ ID NO: 1 inhibited the recruitment of peritoneal cells by RANTES for up to 24 hours whereas the same intraperitoneally administered RANTES homolog was able to inhibit the recruitment of cells for a period of less than 8 hours. Thus, the oral administration of RANTES homologs has been demonstrated to have unexpectedly better bioavailability and/or ability to inhibit the recruitment of cells as compared to other routes of administration (*e.g.*, intraperitoneal administration) for the same RANTES homolog. Accordingly, it is respectfully requested that these indicia of non-obviousness be taken into consideration and that the obviousness-type double patenting rejection of record be withdrawn.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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